REMARKS

This Request for Continued Examination (RCE) is filed under 37 C.F.R. § 1.114. This RCE is being filed prior to the abandonment of the application, as the Notice of Appeal filed under 37 C.F.R. § 1.191 on June 30, 2004 sets a two-month period for response. The amendments to the claims and the new arguments regarding patentability constitute the submission required for an RCE under 37 C.F.R. § 1.114(c). The fee for a RCE under 37 C.F.R. § 1.17(e) of $385.00 accompanies this RCE.

Claims 1-29 are currently pending in the above-identified application and remain for consideration, claims 16-29 having been added by this amendment.

In the Advisory Action mailed June 16, 2004, the Examiner indicated that the previously filed amendment would be entered in the event of an appeal. Accordingly, the claims recited herein reflect the claims as of the entry of that amendment.

Comments made herein as to the status of the claims refer to the status of those claims as set forth in the Advisory Action mailed June 16, 2004.

Claims 3 and 12 had been allowed. Those claims remain without change as the result of the RCE.

Claims 1-2, 4-11, and 13-15 had been rejected under the first paragraph of 35 U.S.C. § 112 as lacking written description in the specification.

Claims 1-2, 4-11, and 13-15 had also been rejected under the first paragraph of 35 U.S.C. § 112 as lacking enablement in the specification.

Reexamination of the application as amended in the RCE, reconsideration of the rejections, and allowance of the claims not already allowed are respectfully requested.

The two-month shortened statutory period subsequent to the Notice of Appeal expires on August 30, 2004. Accordingly, this RCE is being filed in a timely manner.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to be not in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at his earliest possible convenience.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, these amendments introduce no new matter.

A. Amendments to Existing Claims

The amendments to existing claims are made for clarity and definiteness in order to clarify the scope of the claimed invention. Specifically, claim 1 is amended to recite that "the chimeric isoprenoid synthase polypeptide has a conserved amino acid sequence motif of DDXXD that is located in a different position in the chimeric isoprenoid synthase polypeptide than in the naturally-occurring isoprenoid synthase polypeptide." This is supported in the original specification at page 15, lines 15-17, which defines the DDXXD motif within the 5-epi-aristolochene specific domain, and in Figure 6, which shows gene constructs in which the relative position of this 5-amino-acid motif is altered with respect to the arrangement of those domains in the wild-type

synthase genes. Claim 1 is also amended to recite: "wherein the chimeric isoprenoid synthase polypeptide folds into a tertiary structure that results in synthase activity." This requirement is inherent from the recited synthase activity of these constructs, as shown, for example, in Figure 4A for the examples. It is well known that all proteins possess primary, secondary, and tertiary structures, and that tertiary structure must be maintained for the protein to possess its intended function, such as isoprenoid synthase activity. Therefore, the maintenance of tertiary structure is inherent from the isoprenoid synthase activity of the constructs. This synthase activity requires correct folding of the enzyme protein, which, in turn, requires maintenance of the appropriate tertiary structure.

Claim 2 is amended for clarity. This amendment does not alter the scope of the claim but is merely made to place the claim in better form.

Claim 7 is amended similarly to claim 1 to recite: "wherein the chimeric isoprenoid synthase polypeptide folds into a tertiary structure that results in synthase activity." This amendment is made on the same basis and for the same reason as the corresponding amendment to claim 1.

Claim 10 is amended for clarity in a manner analogous to the amendment to claim 2.

B. Newly Added Claims

Claim 16 is equivalent to claim 7, except that it recites the chimeric isoprenoid synthase in the context of a plant cell, as in claim 1. The original claims make it clear that these chimeric isoprenoid synthases can be recited either in the context of a plant cell that contains the required chimeric synthase, or in the context of a transgenic plant, the genome of whose cells contain DNA encoding the required chimeric synthase. Accordingly, claims such as claim 16 are fully supported by the original specification.

Claims 17-19 are equivalent to original claims 9-11, except in the context of a plant cell, as for claim 16.

Claim 20 specifies the products produced by the two domains of the chimeric isoprenoid synthase. These products are recited at page 12, lines 15-18. .

Claim 21 specifies the existence of a third domain, the ratio-determinant domain, located between the domains that control the synthesis of the particular isoprenoid reaction products. The existence of the third domain and its relative placement within the chimeric synthase are recited at page 15, lines 9-11.

Claim 22 specifies that one of the domains in the chimeric synthase is at least the active portion of the TEAS gene from tobacco that catalyzes the synthesis of 5-epi-aristolochene. This is supported by the specification at, e.g., page 9, line 13.

Similarly, claim 23 specifies that one of the domains in the chimeric synthase is at least the active portion of the HVS gene from *Hyoscyamus* that catalyzes the synthesis of vetispiradiene. This is supported by the specification at, e.g., page 9, line 14.

Claim 24 is equivalent to original claim 1, except that it recites the chimeric synthase with an asymmetrically positioned homologous domain in the context of a transgenic plant, rather than in the context of a plant cell. As indicated above, these contexts are equivalent in the present invention and both are fully disclosed and enabled.

Claim 25 is equivalent to original claim 1, except again in the context of a transgenic plant rather than in a plant cell.

Claim 26 is equivalent to new claim 20, except again in the context of a transgenic plant rather than of a plant cell, and is supported by the same language as claim 20.

Claim 27 is equivalent to new claim 21, except again in the context of a transgenic plant. This is supported by the same language as claim 21.

Claims 28-29 are equivalent to new claims 22-23, except again in the context of a transgenic plant. These claims are supported by the same language as claims 22-23.

Accordingly, these amendments introduce no new matter and are fully supported by the specification. Therefore, entry of these amendments is respectfully requested.

II. THE REJECTIONS UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112 FOR LACK OF WRITTEN DESCRIPTION

Claims 1-2, 4-11, and 13-15 had been rejected under the first paragraph of 35 U.S.C. § 112 as lacking written description in the specification. To the extent that the amendments to these claims do not obviate these rejections, they are respectfully traversed.

All that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the

context of nucleic acids, and by analogy, in the context of proteins encoded by nucleic acids, the recitation of structure for the claimed subject matter need not be great in order to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406. Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id.

This basic standard for compliance with the written description requirement under the first paragraph of 35 U.S.C. § 112 is satisfied by the insertion of specific language into the claims reciting a conserved amino acid sequence motif, together with language that specifies the relative position of specific domains in the chimeric synthase incorporated into the plant cell or transgenic plant. There are sufficient relevant identifying characteristics to meet this standard.

The "Guidelines for Examination of Patent Examinations Under the 35 USC § 112 para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001) issued by the United States Patent and Trademark Office, state that the policy goals of the written description requirement are to: (i) clearly convey to the public what was invented; (ii) put the public in possession of what the applicant claims as the invention; and (iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. These policy requirements are met by the amended claims.

Moreover, possession of the claimed invention can be shown by any of: (1) actual reduction to practice; (2) a "clear depiction" of the invention in detailed drawings; or (3) a description of sufficient relevant identifying characteristics. These requirements are met. There is actual reduction to practice in terms of the production of several active chimeric synthase molecules. The actual reduction to practice goes beyond

one specific embodiment. The results recited in the specification indicate that a considerable amount of domain exchange and single-amino-acid mutation is tolerated and is consistent with the enzymatic activity of the chimeric synthases of the invention. This is shown, for example, in Figure 4A, Figure 6, Figure 7, and Figure 8.

These chimeric polypeptides are not defined merely by function; rather, they are defined in terms of specific structural features. These features include the specific domains recited, including the domains that control the synthesis of specific isoprenoid products, and the conserved DDXXD domain. This is sufficient to describe the invention "so that one skilled in the art can recognize what is claimed." Enzo Biochem, Inc. v. Gen-Probe, Inc., 62 U.S.P.Q. 2d 1289, 1293-94 (Fed. Cir. 2002) ("Enzo I"). That standard is clearly met here.

Moreover, it is well-established that an applicant need not disclose every species encompassed by a claim. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

This argument is supported by other results on domain swapping. These results indicate what domains are responsible for particular steps in the enzymatic synthesis of terpenes. These domains are associated with both structural and functional features in the DNA and are correlated with the amino acid sequences encoded by particular exons in the DNA. Thus, the recitation of these domains provides both structural and functional information about the claimed chimeric isoprenoid synthases. This structural and functional information is sufficient to provide a written description of the claimed invention.

In general, the work of Applicants establishes that chimeric isoprenoid synthases that catalyze a spectrum of reaction products not obtained with naturally occurring wild-type isoprenoid synthases can be obtained. These chimeric synthases are obtained by ligating conserved functional domains of different isoprenoid synthases

together, resulting in synthases that can catalyze more than one reaction in isoprenoid synthesis.

Isoprenoid synthase genes are found in a large variety of organisms including bacteria, plants, and fungi. In general, isoprenoid synthase genes, and the proteins encoded by them, demonstrate highly conserved and distinct domain regions. The individual members of the isoprenoid synthase families are multi-domain proteins that catalyze the synthesis of particular biologically active chemical compounds with a wide variety of functional groups. For any particular family member, different protein domains catalyze different steps in the overall synthesis reaction. Each family member catalyzes the synthesis of a different terpenoid compound because each member contains a different collection or arrangement of protein functional domains.

The concept of functional and structural domains within a protein is well known. In general, a domain is a part of the polypeptide chain of a protein molecule that forms a compact globular substructure with more interactions within itself than with other parts of the polypeptide chain. These domains not only have a compact substructure in and of themselves, but they typically carry out a partial activity or a portion of a reaction catalyzed by the protein as an enzyme. Typically, the stability of such a domain toward a denaturant such as heat, guanidinium ions, or urea is not markedly modified by the presence of the rest of the protein.

This leads to the idea that domains can be duplicated or exchanged between proteins to build proteins with different functions, such as the catalysis of different enzymatic reactions, with the maintenance of the structural and functional integrity of the domains. This idea is employed in designing the constructs that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

In many cases, the domains are contiguous or nearly contiguous with exons in a protein where the gene encoding the protein has multiple exons interrupted by non-expressed introns. This suggests that the proteins evolved by adding exons that encoded amino acid sequences having particular functions. The correspondence between exons and functional or structural domains is also employed in designing the constructs that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

This analysis has been applied to the isoprenoid synthases. Swapping regions of the proteins that are contiguous or nearly contiguous between different isoprenoid synthases has led to the identification of functional domains responsible for the terminal enzymatic steps that catalyze the last step in the formation of specific terpenes. For example, work performed on the 5-epi-aristolochene synthase (TEAS) from *Nicotiana tabacum* (the tobacco plant) and the *Hyoscyamus muticus* (the henbane plant) vetispiradiene synthase (HVS) revealed that exon 4 of TEAS and exon 6 of HVS, respectively, were responsible for the reaction product specificity of the synthases. Combining these functional domains resulted in novel enzymes capable of synthesizing new reaction products (U.S. Patent No. 5,824,774).

In another example, the genes for chrysanthemyl diphosphate (CPP) synthase and farnesyl diphosphate (FPP) synthase from sagebrush, *Artemisia tridentata spiciformis*, were also isolated and characterized. These genes for enzymes involved in isoprenoid synthases were also shown to contain five conserved regions found in prenyltransferases that catalyze chain elongation in this family of compounds. Similarly, three full-length cDNAs encoding putative isoprenoid synthases, FDS-1, FDS-2, and FDS-5, with greater than 89% similarity, were isolated from an *Artemisia* cDNA library. These cDNAs were demonstrated to contain conserved domains.

Work subsequent to the filing date of this application demonstrates that these enzymes contain conserved domains that can be reorganized in protein molecules to

provide novel chimeric enzymes. The process by which these conserved domains are reorganized is known as domain swapping and is well known in the art. The process of domain swapping substantially preserves the structural and functional integrity of the domains involved in it. For example, in M. Schalk & R. Croteau, "A Single Amino Acid Substitution (F363I) Converts the Regiochemistry of the Spearmint (-)-Limonene Hydroxylase from a C6- to a C3-Hydroxylase," Proc. Natl. Acad. Sci. 11948-11953 (2000) ("Schalk & Croteau (2000))" (previously made of record), chimeric hydroxylases were generated using a domain-swapping process.

Thus, it is evident from the studies of Applicants and from other work that it was known that isoprenoid synthase genes contained several highly conserved domain regions, and that domain swapping could be practiced on such genes. This work establishes that Applicants had possession of the claimed invention at the time of filing the above-identified patent application and that one of ordinary skill in the art would recognize what is claimed. That is all that is required to meet the written description requirement of the first paragraph of 35 U.S.C. § 112.

The comments previously made by the Examiner with respect to the teachings of H.K. Erickson & C.D. Poulter, "Chrysanthemyl Diphosphate Synthase. The Relationship among Chain Elongation, Branching, and Cyclopropanation Reactions in the Isoprenoid Biosynthetic Pathway," J. Am. Chem. Soc. 125: 6886-6888 (2003) ("Erickson & Poulter (2003)"), are not actually applicable to the constructs at issue here. The reason that the teachings of Erickson & Poulter (2003) are not applicable is that Erickson & Poulter (2003) actually deals with enzymes that catalyze chain elongation or cyclopropanation reactions that extend the length of the isoprenoid molecule precursor. Erickson & Poulter (2003) does not deal with enzymes that catalyze the synthase reactions that form either 5-epi-aristolochene or vetispiradiene from the eudesmane carbocation, their common precursor (Specification, Fig. 3). Neither of these reactions is properly characterized as either a chain elongation, i.e., a condensation reaction that attaches the hydrocarbon moiety of an allylic diphosphate to the double bond in

isopentenyl diphosphate to extend the chain by one isoprenoid unit, or a cyclopropanation, i.e., the joining of two allylic diphosphates to produce a cyclopropylcarbinyl diphosphate. The reactions catalyzed by TEAS or HVS occur later, after the diphosphate moiety has been cleaved from the intermediate, and are in the nature of rearrangements. Thus, there is no basis to apply the findings of Erickson & Poulter (2003) to the constructs of the present invention. Although related to the synthase molecules that are the subject of the present invention, the enzymes that are the subject of Erickson & Poulter (2003) carry out different reactions and are differently organized at the domain level.

Accordingly, in view of the structural features recited, together with the functional characteristics of these chimeric isoprenoid synthases, there is sufficient detail in the specification of this patent application to meet the written description requirement. Therefore, the Examiner is respectfully requested to withdraw this rejection.

III. THE REJECTIONS UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112 FOR LACK OF ENABLEMENT

Claims 1-2, 4-11, and 13-15 had been rejected under the first paragraph of 35 U.S.C. § 112 as lacking enablement. To the extent that the amendments to these claims do not obviate these rejections, they are respectfully traversed.

The Examiner has stated that the specification is enabling for plant cells or transgenic plants comprising chimeric variants of TEAS or HVS, or comprising quiescent synthases, but does not reasonably provide enablement for any chimeric synthase within the scope of the claims. It appears to have been the Examiner's position that, because the specification did not teach all possible nucleic acid molecules encoding functional or nonfunctional domains that could have been used to generate the claimed chimeric proteins, enablement is lacking. The Examiner also has asserted that without appropriate

guidance, the skilled practitioner would not know which domains could be combined in a chimeric protein to yield a functional protein.

The Examiner has further recited Schalk & Croteau (2000) and M.K. El Tamer et al., "Domain Swapping of *Citrus limon* Monoterpene Synthases: Impact on Enzymatic Activity and Product Specificity," Arch. Biochem. Biophys. 411: 196-203 (2003) ("El Tamer et al. (2003") as evidence that enablement is lacking. These references do not support an argument for lack of enablement. Schalk & Croteau (2000) reports on the construction of a total of 20 chimeras. Of these 20 chimeras, a total of 11, or 55%, had detectable hydroxylase activity. The regiospecificity of that hydroxylase activity (i.e., C-3 or C-6 hydroxylation) was determined by the particular domain swapped in. The results of Schalk, in fact, support that there is a reasonable probability of producing an active protein by using domain-swapping procedures analogous to those used in producing chimeric synthases of the claimed invention.

Similarly, El Tamer et al. (2003) used a similar domain-swapping technique to produce chimeric monoterpene synthases. Here, again, a significant proportion of the chimeric synthases were active. Of the 14 chimeric synthases tested, only four were completely inactive, while at least six had significant enzymatic activity of at least about 25% of the wild-type synthases. The results of El Tamer et al. (2003) also fail to support an argument that domain swapping could not produce chimeric synthases with significant enzymatic activity without undue experimentation.

Moreover, the burden of the Patent and Trademark Office to show non-enablement has not been met for this rejection, because the statements cited in the prior Office Action do not counter the actual examples and results cited in the specification. In Schalk & Croteau (2000), the fact that a single amino acid substitution can convert the regioselectivity of the hydroxylase from a C6- to a C3- hydroxylase cannot be taken as proof that domain swapping is likely to result in non-functional enzymes. As recited above, a significant proportion of chimeric hydroxylases produced by domain swapping

in Schalk & Croteau (2000) were functional. The same is true for El Tamer et al. (2003), which studied domain swapping in *Citrus limon* monoterpene synthases.

It is established law with respect to enablement that the specification must be taken as being in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective role of the statements contained in the specification which must be relied upon for enabling support. In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Here, any uncertainty as to the efficacy of the domain swapping method is overcome by the actual teachings of the specification, which recite the preparation of at least fourteen examples of domain-swapped isoprenoid synthases with detectable enzymatic activity. The questions raised in the previous Office Action do not rise to the level of creating doubt as to the objective role of the statements in the specification being relied upon for enabling support of the claimed invention, as required under In re Marzocchi.

Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirements of 35 U.S.C. § 112 are a requirement to properly support such a rejection. The absence of such properly reasoned and supported statements compels withdrawal of this rejection. In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993). The statements relied upon by the Examiner, in view of the actual results obtained in Schalk & Croteau (2000) and El Tamer et al. (2003), fall far short of the reasoned and supported statements required by Wright. The question, from the standpoint of compliance with the enablement requirement of the first paragraph of 35 U.S.C. § 112, is whether the specification, including the examples, enables one of ordinary skill in the art to prepare the required chimeric synthases with appropriate enzymatic activity and incorporate them into plant cells or transgenic plants. The answer, in view of the specification and examples, to this question is undoubtedly affirmative.

The specification need not recite details of the claimed invention where one of ordinary skill in the art would consider these details obvious or well known in the

art. In re Skirvan, 427 F.2d 801, 166 U.S.P.Q. 85 (C.C.P.A. 1970). The quantity of detail permitted to be omitted can be substantial when the state of the art is such that the detail could be readily supplied by one of ordinary skill in the art. This is true even if no working examples are furnished. In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (immunochemistry). It then follows that the presence of working examples, as provided in the specification of the present application, strengthens the case for enablement. These examples are in the form of chimeric isoprenoid synthases produced by domain swapping.

Even should considerable experimentation be required, this does not constitute "undue experimentation" if the experimentation required is routine and the worker is given sufficient guidance. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). Thus, the amount of experimentation that *might* be required does not give rise to a conclusion of lack of enablement. Moreover, complete reproducibility is not required to find enablement. Johns Hopkins University v. CellPro, Inc., 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998). In fact, under the holding of Johns Hopkins University, the fact that some attempts at reproducing the claimed invention fail does not lead to a conclusion of undue experimentation. In Johns Hopkins University, the invention concerned monoclonal antibodies, and attempts to reproduce the claimed invention did not uniformly result in success. The Federal Circuit held that this did not constitute undue experimentation, because a certain amount of experimentation was inherent in the Kohler-Milstein process for producing monoclonal antibodies, and a certain degree of irreproducibility was expected. Id.

The degree of unpredictability must be considered within the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of what is actually claimed is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of

cyanobacteria allowable even though claims were not limited to expression of genes encoding particular Bacillus proteins in view of extensive understanding in the prior art of toxicity of Bacillus proteins). The skill of those of ordinary skill in the art clearly encompasses the preparation and use of chimeric proteins such as those recited in the claims at issue, as well as of plant cells and transgenic plants incorporating DNA encoding such chimeric proteins. This is another strong argument for enablement of the claimed invention.

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer Corp., 946 F.2d 1528, 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This test is clearly met here by the examples of particular chimeric proteins produced by domain swapping and mutagenesis described in the specification and examples of their use.

Moreover, there is no requirement that all compositions within the scope of the claimed methods provide the same degree of efficacy or activity. In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973); In re Fouche, 169 U.S.P.Q. 429 (C.C.P.A. 1971). The fact that some of these chimeric isoprenoid synthases have greater enzymatic activity than others does not mean that undue experimentation exists.

As is frequently the case in enablement questions, a review of the factors set forth by the Federal Circuit in In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), is useful. The Wands factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented: (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present. The conclusion is that a rejection under the first paragraph of 35 U.S.C. § 112 should be withdrawn.

The quantity of experimentation required is not excessive in view of the subject matter. The plant cells and transgenic plants containing DNA encoding chimeric isoprenoid synthases, and their preparation, are described in detail. These teachings require little experimentation to be carried out by one of ordinary skill in the art.

The amount of direction or guidance presented in the specification is substantial. This direction or guidance includes the information, as described above, with respect to the methods for the preparation of plant cells and transgenic plants containing DNA encoding chimeric isoprenoid synthases. Moreover, as indicated above, a substantial number of successful working examples is present. The exact methods used are described in detail.

The nature of the invention is such that undue experimentation is not present, when the scope of the claimed invention is taken into account. The claimed invention, from the standpoint of enablement, is of a relatively restricted scope. Moreover, the functional language recited in claims 1and 7 must be taken into account in evaluating the existence of enablement. In re Halleck, 422 F.2d 911, 164 U.S.P.Q. 647 (C.C.P.A. 1970). These are not claims for which a degree of extrapolation is required such that the extrapolation would lead to a conclusion of undue experimentation based on the burden placed on one of ordinary skill in the art to achieve enablement within the scope of the claimed invention. Compare In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (enablement found even though no working examples present) with In re Fisher, 427 F.2d 833, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg, with no upper limit, when specification disclosed preparation of ACTH of potency between 1.11 and

2.30 international units/mg). Here, the scope of the protection sought is relatively circumscribed and the degree of experimentation required is minimal.

The state of the prior art does not suggest an exceptional degree of unpredictability with respect to the activity of chimeric isoprenoid synthases. Although considerations relating to folding of such chimeric proteins do exist, there is sufficient secondary and tertiary structure retained on a domain-by-domain basis to make a reasonable prediction about the structure and activity of the chimeric isoprenoid synthases that are incorporated into the plant cells and transgenic plants of the present invention.

The relative skill of those in the art is high. This invention is directed to biochemists, microbiologists, and cell biologists, typically with a Ph.D. or other advanced degree in the relevant discipline.

The predictability or unpredictability of the art was discussed above. As indicated, the degree of unpredictability in the folding and, thus, the activity, of chimeric isoprenoid synthases is reduced by the existence of domains in these proteins with a largely self-contained structure.

The breadth of the claims does not argue for lack of enablement. The claims contain sufficient structure that one of ordinary skill in the art could predict the activity of these chimeric proteins, and undue experimentation would not be required.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d at 737, 8 U.S.P.Q. 2d at 1404. Wands involved monoclonal antibodies produced by hybridomas. The monoclonal

antibodies had to have a certain degree of affinity toward their corresponding antigen. Of 143 hybridomas produced, only 9 were screened further, and of those 9, only four were found to fall within the scope of the claimed invention. This was sufficient to find enablement in the technology under consideration. The success rate of those hybridomas actually tested, 44%, is very similar to the success rate for enzymatic activity of chimeric isoprenoid synthases or hydrolases found in Schalk & Croteau (2000) and El Tamer et al. (2003). The fact that some chimeric isoprenoid synthases might not fold correctly does not suggest that the working examples do not yield enablement of the claimed invention. This evidence strongly indicates that the amount of experimentation required to reproduce the claimed subject matter would be routine and not undue.

As long as the specification discloses at least one method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claimed invention, the enablement requirement of the first paragraph of 35 U.S.C. § 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). That test is met here in view of the teachings of the specification, including a number of working examples.

The situation here is analogous to that in Wands. The claims are of such a scope that one of ordinary skill in the art could use the claimed invention with a reasonable probability of success. There is no requirement that all chimeric isoprenoid synthases fold correctly to preserve enzymatic activity, but there is sufficient evidence that at least a significant proportion of them will do so.

Accordingly, the Examiner is respectfully requested to withdraw this rejection as applied to the amended claims.

Respectfully submitted,

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